Letter to Editor:

Comment on the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project

Stephen T McSorley[1], Dinesh Talwar[2], Donald C McMillan[1]

1. Academic Unit of Surgery, School of Medicine, University of Glasgow, Glasgow, UK
2. The Scottish Trace Elements and Micronutrients Reference Laboratory, Department of Clinical Biochemistry, Glasgow Royal Infirmary, Glasgow G4 0SF.

Corresponding author:

Mr Stephen McSorley, Clinical Research Fellow

Level 2, New Lister Building, Glasgow Royal Infirmary, Glasgow, UK

Postcode: G31 2ER

Tel: 0141 211 8675

Email: s.mcsorley@doctors.org.uk

Conflict of interest/Disclosure: none

Dear Sir,

We read with interest the recent series of publications of the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project (1-4). These publications highlight the perturbation of plasma measures of iron status and anemia as part of the systemic inflammatory response in a variety of cohorts including pre-school children and women of reproductive age (4). This perturbation has long been recognised (5-6). However, it is only recently that the magnitude of the effect has been well described in large numbers of patient observations (7). There have been two main approaches to the confounding effect of the systemic inflammatory response on the measurement of iron status. The first is to develop other measurements of iron status that are not affected by systemic inflammation. The second is to adjust measurement of iron status and anemia using measures of systemic inflammation (8).

In the BRINDA publications this second approach has been carried out using C-reactive protein (CRP), and α-1-acid glycoprotein (AGP), two positive acute phase proteins of varying half-life. They reported significant differences in the prevalence of depleted iron stores based on serum ferritin criteria (1). When serum ferritin was examined in women of reproductive age there was a significant difference in the proportion of patients meeting criteria for iron deficiency (<15 μg/L) in the lowest and highest decile of both CRP (29% and 6% respectively) and AGP (26% and 8% respectively). In addition, when women of reproductive age were grouped by phase of inflammation using the combination of CRP and AGP, there was as significant difference in the mean lowest (34.9 μg/L, 95% CI 25.7-47.4, in "reference" group [CRP ≤5mg/L and AGP ≤1g/L]) and highest ferritin concentration (59.2 μg/L, 95% CI 48.5-72.2 in "early convalescence" group [CRP >5mg/L and AGP >1g/L]). Furthermore, the authors show that measures of iron status are altered below currently clinically relevant threshold values for both CRP and AGP and so propose that the use of a

regression based correction factor should provide a more accurate assessment of true iron status in the context of systemic inflammation (1). However, AGP is not routinely available as a measure of systemic inflammation in the clinical setting. In the BRINDA project paper the authors propose the continued and expanded use of AGP as a measure of the phase and magnitude of systemic inflammation. However, as they themselves note, "…CRP is the more routinely measured and should continue to be measured along with AGP…", in part as it is not routinely used in clinical practice (1). In addition, the authors also discuss in an earlier publication, the problem associated with the calculation of regression based correction factors caused by serum micronutrient concentrations that do not necessarily "move in synchrony" with the CRP and AGP defined phases of inflammation (10).

Perhaps a better approach would be to use the combination of CRP and albumin, since both are independently associated with measures of iron status, and are routinely available. We recently published an observational study using such a method in a large mixed cohort of 16,552 adult patients in the UK (9). Patients were stratified by the magnitude of the systemic inflammatory response using both CRP and albumin as follows; group 1: CRP <10mg/L and albumin >35g/L, group 2: CRP11-80mg/L and albumin 25-35mg/L, and group 3: CRP >80mg/L and albumin <25g/L. When serum ferritin was compared amongst the 3 groups the median concentration was 77, 173 and 445 μg/L respectively ($p<0.001$). Furthermore, there was a significant difference in the proportion of patients meeting criteria for iron deficiency (<15 μg/L, 13%, 3% and 0% respectively, $p=0.001$) or iron excess (M>300 μg/L F>50 μg/L, 21%, 38% and 75% respectively, $p<0.001$). When transferrin saturation was compared amongst the 3 groups there was a significant difference in the proportion of patients meeting criteria for iron deficiency (TSAT <10%, 15%, 39% and 53% respectively, $p<0.001$) or iron excess (TSAT M>55% F>50%, 7%, 5% and 5% respectively, $p<0.001$).

Given that serum albumin in combination with CRP has been shown to both stratify the magnitude of the systemic inflammatory response, is associated with common measures of iron status, and is routinely clinically available, it might be useful to explore the calculation of such proposed regression based correction factors using the combination of CRP and albumin rather than AGP. With the significant interest in iron status in clinical practice, including the ongoing clinical trials of parenteral iron regimens in patients undergoing elective surgery deemed to be iron deficient, such an approach could have a considerable impact on the requirements for such treatments, and related therapies, including allogeneic blood transfusion.

References:

1. Namaste SM, Rohner F, Huang J, Bhushan NL, Flores-Ayala R, Kupka R, Mei Z, Rawat R, Williams AM, Raiten DJ et al. Adjusting ferritin concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr 2017 doi: 10.3945/ajcn.116.141762 [Epub ahead of print]
2. Adjusting soluble transferrin receptor concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr 2017 doi: 10.3945/ajcn.116.142232 [Epub ahead of print]
3. Adjusting total body iron for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr 2017 doi:10.3945/ajcn.116.142307 [Epub ahead of print]
4. Methodologic approach for the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr 2017 doi:10.3945/ajcn.116.142273 [Epub ahead of print]
5. Fraser WD, Taggart DP, Fell GS, Lyon TD, Wheatley D, Garden OJ, Shenkin A. Changes in iron, zinc, and copper concentrations in serum and their binding to transport proteins after cholecystectomy and cardiac surgery. Clin Chem 1989;35(11):2243-2247
6. Galloway P, McMillan DC, Sattar N. Effect of the inflammatory response on trace element and vitamin status. Ann Clin Biochem 2000;37:289-297
7. Duncan A, Talwar D, McMilla DC, Stefanowicz F, O'Reilly DS. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements. Am J Clin Nutr 2012;95:64-71

8. Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP. Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis. Am J Clin Nutr 2011;92:546-555
9. McSorley ST, Jones I, McMillan DC, Talwar D. Quantitative data on the magnitude of the systemic inflammatory response and its relationship with serum measures of iron status. Transl Res 2016;176:119-126
10. Thurnham DI, Northrop-Clewes CA. Inflammation and biomarkers of micronutrient status. Curr Opin Clin Nutr Metab Care 2016, 19:458–463